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**APPLICATION FOR UNITED STATES PATENT**

**TITLE:** TISSUE AUGMENTATION MATERIAL AND METHOD  
**INVENTORS:** WILLIAM G. HUBBARD  
TIMOTHY R. DEVINE

**FOLEY & LARDNER**  
ONE IBM PLAZA  
SUITE 3300  
330 N. WABASH AVENUE  
CHICAGO, IL 60611  
Telephone: (312) 755-1900  
Facsimile: (312) 755-1925

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## TISSUE AUGMENTATION MATERIAL AND METHOD

### Field of the Invention

This invention relates to biocompatible compositions for soft tissue augmentation more specifically urethral sphincter augmentation for treatment of incontinence, for filling soft tissue voids or creating soft tissue blebs, for mammary implants, and for the treatment of unilateral vocal cord paralysis.

This invention also relates to a gel carrier for the biocompatible compositions.

### Background of the Invention

Examples of biocompatible materials that have been proposed for use in augmenting soft tissue in the practice of plastic and reconstructive surgery, include collagen, gelatin beads, beads of natural or synthetic polymers such as polytetrafluoroethylene, silicone rubber and various hydrogel polymers, such as polyacrylonitrile-polyacrylamide hydrogels.

Most often, the biomaterials are delivered to the tissue site where augmentation is desired by means of an injectable composition which comprises the biomaterial and a biocompatible fluid that acts as a lubricant to improve the injectability of the biomaterial suspension. The injectable biomaterial compositions can be introduced into the tissue site by injection from a syringe intradermally or subcutaneously into humans or other mammals to augment soft tissue, to correct congenital anomalies, acquired defects or cosmetic defects.

They may also be injected into internal tissues such as tissue defining sphincters to augment such tissue in the treatment of incontinence, and for the treatment of unilateral vocal cord paralysis.

U.K Patent Application No. 2,227,176 to Ersek et al, relates to a microimplantation method for filling depressed scars, unsymmetrical orbital floors and superficial bone defects in reconstructive surgery procedures using microparticles of about 20 to 3,000 microns which may be injected with an appropriate physiologic vehicle and hypodermic needle and syringe in a predetermined locus such as the base of depressed scars, beneath skin areas of depression and beneath perichondrium or periosteum in surface irregularities of bone and cartilage. Textured microparticles can be used, including silicone, polytetrafluoroethylene, ceramics or other inert substances. In those instances wherein the requirement is for hard substances, biocompatible material such as calcium salts including hydroxyapatite or crystalline materials, biocompatible ceramics, biocompatible metals such as stainless steel particles or glass may be utilized. Appropriate physiological vehicles have been suggested, including saline, various starches, polysaccharides, and organic oils or fluids.

U. S. Patent No. 4,803,075 to Wallace et al, relates to an injectable implant composition for soft tissue augmentation comprising an aqueous suspension of a particulate biocompatible natural or

synthetic polymer and a lubricant to improve the injectability of the biomaterial suspension.

U. S. Patent No. 4,837,285 to Berg et al., relates to a collagen-based composition for augmenting soft tissue repair, wherein the collagen is in the form of resorbable matrix beads having an average pore size of about 50 to 350 microns, with the collagen comprising up to about 10% by volume of the beads.

U. S. Patent No. 4,280,954 to Yannas et al., relates to a collagen-based composition for surgical use formed by contacting collagen with a mucopolysaccharide under conditions at which they form a reaction product and subsequently covalently crosslinking the reaction product.

U. S. Patent No. 4,352,883 to Lim discloses a method for encapsulating a core material, in the form of living tissue or individual cells, by forming a capsule of polysaccharide gums which can be gelled to form a shape retaining mass by being exposed to a change in conditions such as a pH change or by being exposed to multivalent cations such as calcium.

Namiki, "Application of Teflon Paste for Urinary Incontinence-Report of Two Cases," Urol. Int., Vol. 39, pp. 280-282, (1984), discloses the use of a polytetrafluoroethylene paste injection in the subdermal area to treat urinary incontinence.

Drobeck et al, "Histologic Observation of Soft Tissue Responses to Implanted, Multifaceted Particles and Discs of Hydroxylapatite," Journal of Oral Maxillofacial Surgery, Vol. 42, pp. 143-149,

(1984), discloses that the effects on soft tissue of long and short term implants of ceramic hydroxylapatite implanted subcutaneously in rats and subcutaneously and subperiosteally in dogs. The inventions consisted of implanting hydroxylapatite in various sizes and shapes for time periods ranging from seven days to six years to determine whether migration and/or inflammation occurred.

Misiek et al., "Soft Tissue Responses to Hydroxylapatite Particles of Different Shapes," Journal of Oral Maxillofacial Surgery, Vol. 42, pp. 150-160, (1984), discloses that the implantation of hydroxylapatite in the form of sharp edged particles or rounded particles in the buccal soft tissue pouches produced inflammatory response at the implant sites with both particle shapes. Each of the particles weighed 0.5 grams. However, inflammation resolved at a faster rate at the sites implanted with the rounded hydroxylapatite particles.

Shimizu, "Subcutaneous Tissue Responses in Rats to Injection of Fine Particles of Synthetic Hydroxyapatite Ceramic," Biomedical Research, Vol. 9, No. 2, pp. 95-111 (1988), discloses that subcutaneous injections of fine particles of hydroxyapatite ranging in diameter from about 0.65 to a few microns and scattered in the tissue were phagocytized by macrophages in extremely early stages. In contrast, larger particles measuring several microns in diameter were not phagocytized, but were surrounded by numerous macrophages and multinucleated giant cells. It was also observed

that the small tissue responses to hydroxyapatite particles were essentially a non-specific foreign body reaction without any cell or tissue damage.

R. A. Appell, "The Artificial Urinary Sphincter and Periurethral Injections," Obstetrics and Gynecology Report Vol. 2, No. 3, pp. 334-342, (1990), is a survey article disclosing various means of treating urethral sphincteric incompetence, including the use of injectables such as polytetrafluoroethylene micropolymer particles of about 4 to 100 microns in size in irregular shapes, with glycerin and polysorbate. Another periurethral injectable means consists of highly purified bovine dermal collagen that is crosslinked with glutaraldehyde and dispersed in phosphate-buffered physiologic saline.

Politano et al, "Periurethral Teflon Injection for Urinary Incontinence," The Journal of Urology, Vol. 111, pp. 180-183 (1974), discloses the use of Polytetrafluoroethylene paste injected into the urethra and the periurethral tissues to add bulk to these tissues to restore urinary control in both female and male patients having urinary incontinence.

Malizia et al, "Migration and Granulomatous Reaction After Periurethral Injection of Polytef (Teflon)," Journal of the American Medical Association, Vol. 251, No. 24, pp. 3277-3281, June 22-29 (1984), discloses that although patients with urinary incontinence have been treated successfully by periurethral injection of polytetrafluoroethylene paste, a study in continent animals demonstrates

migration of the polytetrafluoroethylene particles from the inspection site.

5           Claes et al, "Pulmonary Migration Following Periurethral Polytetrafluoroethylene Injection for Urinary Incontinence," The Journal of Urology, Vol. 142, pp. 821-2, (September 1989), confirms the finding of Malizia in reporting a case of clinically significant migration of polytetrafluoroethylene paste particles to the lungs after periurethral injection.

10           Ersek et al, "Bioplastique: A New Textured Copolymer Microparticle Promises Permanence in Soft-Tissue Augmentation," Plastic and Reconstructive Surgery, Vol. 87, No. 4, pp. 693-702, (April 1991), discloses the use of a biphasic copolymer made of fully polymerized and vulcanized methylmethyldpolysiloxane mixed with a plasdone hydrogel, and used in reconstructing cleft lips, depressed scars of chicken pox and indentations resulting from liposuction, glabella frown wrinkles and soft tissue augmentation of thin lips. The biphasic copolymer particles were found to neither migrate nor become absorbed by the body were textured and had particle sizes varying from 100 to 600 microns.

15           Lemperle et al. "PMMA Microspheres for Intradermal Implantation: Part I. Animal Research," Annals of Plastic Surgery, Vol. 26, No. 1, pp. 57-63, (1991), discloses the use of polymethylmethacrylate microspheres having particle sizes of 10 to 63 microns in diameter used for correction of small deficiencies within the dermal corium to treat wrinkles and acne scars.

Kresa et al, "Hydron Gel Implants in Vocal Cords," Otolaryngology Head and Neck Surgery, Vol. 98, No. 3, pp. 242-245, (March 1988), discloses a method for treating vocal cord adjustment where there is insufficient closure of the glottis which comprises introducing a shaped implant of a hydrophilic gel that has been previously dried to a glassy, hard state, into the vocal cord.

Hirano et al, "Transcutaneous Intrafold Injection for Unilateral Vocal Cord Paralysis: Functional Results," Ann. Otol. Rhinol. Laryngol., Vol. 99, pp. 598-604 (1990), discloses the technique of transcutaneous intrafold silicone injection in treating glottic incompetence caused by unilateral vocal fold paralysis. The silicone injection is given under a local anesthetic with the patient in a supine position, wherein the needle is inserted through the cricothyroid space.

Hill et al, "Autologous Fat Injection for Vocal Cord Medialization in the Canine Larynx," Laryngoscope, Vol. 101, pp. 344-348 (April 1991), discloses the use of autologous fat as an alternative to Teflon® collagen as the implantable material in vocal cord medialization, with a view to its use as an alternative to non-autologous injectable material in vocal cord augmentation.

Mikaelian et al, "Lipoinjection for Unilateral Vocal Cord Paralysis," Laryngoscope, Vol. 101, pp. 4654-68 (May 1991), discloses that the commonly used procedure of injecting Teflon® paste to improve the caliber of voice in unilateral vocal cord paralysis has a number of drawbacks, including respiratory

obstruction from overinjected Teflon® and unsatisfactory voice quality. In this procedure, lipoinjection of fat commonly obtained from the abdominal wall appears to impart a soft bulkiness to the injected cord while allowing it to retain its vibratory qualities. The injected fat is an autologous material which can be retrieved if excessively overinjected.

Strasnick et al, "Transcutaneous Teflon® Injection for Unilateral Vocal Cord Paralysis: An Update," Laryngoscope, Vol. 101, pp. 785-787 (July 1991), discloses the procedure of Teflon® injection to restore glottic competence in cases of paralytic dysphonia.

#### Summary of the Invention

In accordance with the present invention, there is provided a permanent, biocompatible material for soft tissue augmentation, and methods for its use. There is also provided in accordance with the present invention a gel carrier which is particularly advantageous for the administration of the biocompatible material to the desired tissue augmentation site.

The biocompatible material comprises a matrix of smooth, rounded, substantially spherical, finely divided particles of a biocompatible ceramic material, close to or in contact with each other, which provide a scaffold or lattice for autogenous, three dimensional, randomly oriented, non-scar soft tissue growth at the augmentation site. The augmentation material can be homogeneously suspended, for example, in a biocompatible,

resorbable lubricious gel carrier comprising, e.g.,  
a polysaccharide. This serves to improve the  
delivery of the augmentation material by injection  
to the tissue site where augmentation is desired.  
5 The augmentation material is especially suitable for  
urethral sphincter augmentation, for treatment of  
incontinence, for filling soft tissue voids, for  
creating soft tissue blebs, for the treatment of  
unilateral vocal cord paralysis, and for mammary  
10 implants. It can be injected intradermally or  
subcutaneously or can be implanted.

Description of the Drawings

In the accompanying drawings,

15 FIGURE 1 is a photomicrograph of smooth, round  
calcium hydroxyapatite particles at 40x  
magnification;

FIGURE 2 is a photomicrograph of a  
histological section of rabbit tissue at 50x  
magnification showing fibroblastic infiltration.

20 FIGURE 3 is a graph of the viscosity of the gel  
and augmentation media both before and after  
sterilization.

Description of the Preferred Embodiments

25 In instances of urinary incontinence, such as  
stress incontinence in women, or after a  
prostatectomy in men, it is necessary to compress  
the urethra to assist the sphincter muscle in  
closing to avoid leakage of urine from the bladder.

30 The soft tissue augmentation material of the  
present invention comprises an injection system  
which can be used to add bulk and localize  
compression to the sphincter muscle/urethra, thereby

reducing the lumen size through one or more injections of the augmentation material and thus substantially reduce or eliminate urinary stress incontinence due to incompetent sphincters in females and males.

The augmentation material can also be used in filling and smoothing out soft tissue defects such as pock marks or scars. Further use for the augmentation material can be for intracordal injections of the laryngeal voice generator by changing the shape of this soft tissue mass. The procedure involves delivering the augmentation material to the site of treatment, preferably by injection. The augmentation material or gel can also be used for mammary implants.

The inventive augmentation material comprises smooth rounded, substantially spherical, particles of a ceramic material. The term "substantially spherical" refers to the fact that while some of the present particles may be spheres, most of the particles of the present invention are sphere-like in their shape, i.e., they are spheroidal. FIGURE 1 is illustrative of these spheroidal or substantially spherical characteristics. The terms "rounded" or "smooth, rounded" as used herein refers to the fact even though the present particles are not perfect spheres, they do not have any sharp or angular edges. The particles must be sufficiently large so as to avoid phagocytosis, as is further discussed below. As an upper limit the particles can be any size suitable for the desired soft tissue augmentation. However, it is understood that for

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introduction by injection the upper limit on  
particle size will be dictated by the particular  
injection equipment employed. That is, the  
particles must be sufficiently small so as to avoid  
5 aggregation and clogging of the syringe when being  
injected. A typical range for injection is from  
about 35 to 150 microns, preferably in a narrow  
particle size range extending not more than about 35  
10 microns, and more preferably extending not more than  
about 10 to 30 microns, and-most preferably having  
substantially equivalent particle sizes. For  
example, the ceramic material can have a uniform  
particle size distribution of about 35 to 65  
15 microns, or 75 to 100 microns or 100 to 125 microns.  
These are meant to be exemplary and not limiting.  
Other narrow particle size ranges within the overall  
size range of 35 to 150 microns can also be used.  
In discussing these ranges, it should be understood  
20 that as a practical matter, a small amount of  
particles outside the desired range may be present  
in a sample of the present augmentation material.  
However, most of the particles in any given sample  
should be within the desired range. Preferably, 90%  
25 of the particles are within the desired range and  
most preferably 95-99% are within the range.

The finely divided ceramic augmentation  
material is substantially non-resorbable so that  
repetitious corrections are not necessary. By  
"substantially non-resorbable" is meant that  
30 although some dissolution of the augmentation  
material may take place over time, it is  
sufficiently slow so as to allow for replacement

with growing tissue cells. There is no antigenic response because there are no amino acids as in collagen and fibrinogen. The ceramic material is highly biocompatible and can be injected through an 5  
18 gauge or smaller opening syringe.

The preferred ceramic material is calcium hydroxyapatite, also known as basic calcium orthophosphate, or calcium hydroxylapatite, and is the natural mineral phase of teeth and bones. As an 10  
implant material, granular calcium hydroxyapatite, which is a sintered polycrystalline composite of calcium phosphate, has proven to be highly compatible in tissue.

One method for preparing dense, rounded or 15  
substantially spherical ceramic particles such as calcium hydroxyapatite is by spray drying a slurry of about 20 to 40 weight % submicron particle size calcium hydroxyapatite. This material is commercially available or can be prepared by means 20  
known in the art such as by low temperature crystallization methods, hydrothermal crystallization methods, solid-solid reaction and the like. The slurry can also include processing additives such as wetting agents and binders, on the order of about 1 to 5 weight %. Suitable wetting 25  
agents include polysorbate, sodium oxalate, ammonium polyelectrolyte. Suitable binders include polyvinyl alcohol, dextrin or carbowax.

The slurry is spray dried by pumping it through 30  
a nozzle to form globules that are forced through a column of heated air to remove the moisture. The agglomerated particles dry in substantially

spherical shape and are collected at one end of the heated column.

The substantially spherical particles are then sintered in a crucible at temperatures of about 5 1050 to 1200<sup>0</sup>C for at least one hour. To minimize further agglomeration, a presintering operation at about 800 to 1000<sup>0</sup>C for about one hour can be employed.

10 After the presintering operation, the globular particles can be agitated or rolled to prevent the individual particles from sticking or clumping together. A rotary calcining furnace can be used for this purpose. This type of furnace rotates so that the agglomerated particles roll over one another during the sintering process thereby minimizing the clumping together of the particles. 15 A commercial source of such spray dried particles is CeraMed Corp., Lakewood, Colorado.

20 An alternative method for forming dense, spherical particles is by rotary agglomeration, wherein the fine, submicron ceramic particles, such as calcium hydroxyapatite, are placed on a large diameter rotating bowl that is at least about 3 feet in diameter.

25 The bowl is rotated on its axis at an angle of approximately thirty degrees, with its speed and angle of rotation adjusted so that the submicron particles roll across the face of the bowl. A fine spray of binder solution, such as those described above, is then sprayed on the particles at a rate which just wets the particles. The rolling action 30 across the face of the bowl and the addition of the

binder solution causes the particles to form small  
5 rolling agglomerates that grow in size as the  
operation continues. The operation is comparable to  
forming a large ball of snow by rolling a small  
snowball down a hill. The operating conditions,  
such as the size of bowl, speed of rotation, angle  
of rotation and amount of spray used which define  
the size and density of the agglomerates formed, are  
well known to those skilled in the art. The  
10 agglomerated spherical particles can then be  
sintered in a manner similar to the spray dried  
agglomerates.

The resulting sintered spherical particles can  
then be separated and classified by size by means of  
15 well known sieving operations through specifically  
sized mesh screens. The particle size distribution  
and density can also be evaluated to ensure  
suitability for a particular application. A  
commercial source of such rotary agglomerated  
20 particles is CAM Implants, Leiden, The Netherlands.

Further surface refining or smoothing can be  
accomplished by a milling operation, such as ball  
milling. Extra mini-grinding media can be used, but  
25 to minimize contamination, the spherical particles  
can be milled on themselves. This can be done in a  
standard jar mill or an inclined rotation mill by  
adding sufficient amounts of purified water to the  
particles to ensure that the particles roll evenly  
over each other. This can be done for long periods  
30 such as several days to make the surface smooth on  
the round agglomerates. If the starting  
agglomerates are not round, they can be made smooth

but not round by rolling. Irregularly shaped agglomerates, although having a smooth surface, can jam, obstruct or significantly increase the injection force on a syringe needle when injected into tissue.

The agglomerated spherical particles can also be washed free of small particles by using an inclined rotation mill. This can be done by placing the agglomerates in the mill with purified water and rolled for a sufficient time, such as one hour. The supernate is then poured off and more purified water is added. The process is repeated until the supernate is relatively clear after a rotating cycle, and usually takes about three or four operations.

The methods described above are suitable for any ceramic materials which may be employed.

A smooth surface on the individual round, spherical particles is important to reduce and minimize surface porosity. Surface smoothness can be improved by finishing operations known in the art, such as surface milling and the like. It is preferred that such smoothing operations be capable of minimizing surface irregularities on the individual particles so that the surface appears similar to that of a smooth round bead when viewed under a microscope at 40x magnification. This is apparent from FIGURE 1, which is a photomicrograph of calcium hydroxyapatite particles having a particle size distribution of 38 to 63 microns. The smooth, round substantially spherical and non-porous surface is readily evident.

The ceramic particles are preferably smooth, hard, rounded particles, having a density on the order of about 75 to 100%, and preferably about 95 to 100% of the theoretical density of desired ceramic material, e.g., calcium hydroxyapatite. The finishing operations can also minimize the surface porosity of the calcium hydroxyapatite particles to less than about 30%, and preferably less than about 10%. This is preferred, because by minimizing surface porosity, particles with smooth surfaces can be obtained, thereby eliminating -jagged, irregular surfaces and maximizing the ability of the smooth, round particles to flow easily in contact with each other.

Although this invention is described in terms of calcium hydroxyapatite, other suitable materials useful herein include, but are not limited to, calcium phosphate-based materials, alumina-based materials and the like. Examples include, but are not limited to, tetracalcium phosphate, calcium pyrophosphate, tricalcium phosphate, octacalcium phosphate, calcium fluorapatite, calcium carbonate apatite, and combinations thereof. Other equivalent calcium based compositions can also be used such as calcium carbonate, and the like.

As noted, the individual ceramic particles used in the present invention have a generally smooth, round, preferably spherical shape, in contrast to particles with more textured porous surfaces or openings, and having jagged, irregular shapes or shapes with straight edges. The smooth round shape enables the ceramic particles to be more easily

extruded and to flow with reduced friction from a  
syringe into the tissue site where soft tissue  
augmentation is desired. Once at the tissue site,  
the ceramic particles provide a matrix or  
scaffolding for autogenous tissue growth.

As mentioned above, particle sizes in the range  
of about 35 to 150 microns are optimal to minimize  
the possibility of particle migration by  
phagocytosis and to facilitate injectability.  
Phagocytosis occurs where smaller particles on the  
order of 15 microns or less become engulfed by the  
cells and removed by the lymphatic system from the  
site where the augmentation material has been  
introduced into the tissues, generally by injection.

At the lower end, particles greater than 15  
microns and typically 35 microns or above are too  
large to be phagocytosized, and can be easily  
separated by known sizing techniques. Thus, it is  
relatively simple to produce the narrow or  
equivalent particle size ranges that are most  
desirable for use in this invention.

It is also desirable to use a narrow or  
equivalent particle size range of ceramic particles  
due to the fact that a distribution of such smooth,  
round, substantially spherical particles reduces  
friction, and facilitates the ease of injecting the  
particles by needle from a syringe into the skin  
tissue at the desired augmentation site. This is in  
contrast to the use of the more porous, textured,  
irregularly shaped particles which tend to increase  
the frictional forces, and are much more difficult  
to deliver by injection.

As discussed above, the particle size distribution, or range of particle sizes of the ceramic material within the overall range of 35 to 150 microns is preferably minimized to a more narrow or equivalent particle size range. This maximizes the intraparticle void volume, or interstitial volume, into which autogenous tissue growth, stimulated by the presence of the augmentation material, can occur. A greater interstitial volume exists between particles that are equivalent in size, compared with particles having a variable size distribution. In the context of this invention, the interstitial volume is the void space existing between particles of the augmentation material that are close to or in contact with each other.

For example, in crystalline lattice structures such as face centered cubic, body centered cubic and simple cubic, the percentage of interstitial void space, known as the atomic packing factor, is 26%, 33%, and 48%, respectively. This is independent of the diameter of the atom or in this case, the particle. Since the ceramic particles never pack as tightly as the atoms in a crystalline lattice structure, the void volume would be even greater, thereby maximizing the growth of autogenous tissue.

To extend the analogy of the crystalline structure a step further, the interstitial opening defines the maximum size that a particle can fit into a normally occurring void space in the structure. The largest interstitial space is about 0.4 times the size of the mean ceramic particle in the particle size distribution.

Thus, if the particle size distribution is about 35 to 65 microns, the mean particle size would be 50 microns. The largest interstitial space would be  $50 \times 0.4 = 20$  microns. Since no 20 micron size particles exist in the distribution, packing would be minimized. Similarly, with a particle size distribution of 75 to 125 microns, the mean particle size is 100 microns, and the largest interstitial space would be  $100 \times 0.4 = 40$  microns. Since no 40 micron particles exist in the distribution, packing would also be minimized. Therefore, if the ceramic particles are restricted to a narrow particle size range or equivalent size distribution, there will be a maximizing of the void volume into which the autogenous tissue can grow.

Other suitable particle size distribution ranges include 35 to 40 microns, 62 to 74 microns and 125 to 149 microns, however, any other correspondingly narrow ranges can also be used.

In contrast, where there is a wide particle size distribution, there is a greater tendency for the particles to become densely packed since the smaller particles tend to group or migrate into the spaces between the larger particles. This results in less interstitial space available between the particles for the autogenous tissue such as fibroblasts and chondroblasts to infiltrate and grow.

The tissue growth where the augmentation material has a wide particle size distribution is denser and harder, because of the packing effect which occurs between the large and small particles.

In contrast, the use of particles equivalent in size, or having a narrow particle size range of uniformly distributed particles increases the intraparticle void volume. This enables a maximum amount of autogenous or three dimensional randomly oriented non-scar soft tissue ingrowth to infiltrate the space or interstices between the particles. The more interstitial space that is available makes it more likely that the subsequent autogenous tissue growth stimulated by the presence of the augmentation material into the matrix or scaffolding provided by the augmentation material will closely resemble the original tissue in the immediate vicinity or locus of augmentation.

The process of soft tissue augmentation can occur by injecting or implanting the biocompatible augmentation material comprising the desired particle sizes of the desired ceramic material into the tissue at the desired augmentation site to form a bleb or blister. The subsequent autogenous tissue growth into the matrix provided by the augmentation material will most closely resemble the surrounding tissue in texture and properties. This is in contrast to that which occurs using known state-of-the-art procedures, where foreign body response is known to occur, typically with Teflon® augmentation where granulomas have been known to form.

Foreign body response is the body reaction to a foreign material. A typical foreign body tissue response is the appearance of polymorphonuclear leukocytes near the material followed by macrophages. If the material is nonbioreactive,

such as silicone, only a thin collagenous encapsulation tissue forms. If the material is an irritant, inflammation will occur and this will ultimately result in granulation tissue formation.

5 In the case of ceramic materials such as calcium hydroxyapatite, there is excellent biocompatibility resulting in tissue cell growth directly on the surface of the particles with a minimum of, or substantially no encapsulation.

10 Autogenous tissue is defined herein as any tissue at a specific defined location in the body, whose growth is stimulated by the presence of the matrix of the biocompatible augmentation material at the site where soft tissue augmentation is desired.

15 Such autogenous tissue from augmentation in the area of the urethral sphincter would resemble existing tissue in the urethral sphincter. Autogenous tissue from augmentation in the larynx would resemble existing tissue in the glottis where the vocal apparatus of the larynx is located. Autogenous tissue from breast augmentation would resemble existing tissue in the mammarys, and so on.

20 Autogenous tissue in the case of intradermal injections would resemble the dermis. In a similar manner, the augmentation material, by providing a three dimensional lattice can be used in surgical incisions or trauma to avoid linear, layered contractile scar formation.

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30 As discussed above, the calcium hydroxyapatite particles used as the augmentation material are biocompatible and substantially non-resorbable. Thus, the soft tissue augmentation procedure is

permanent. Moreover, the use of calcium hydroxyapatite does not require the strict rigorous precautions that are necessary when using other augmentation materials such as collagen which need refrigeration for storage, shipping and antigenicity testing.

The rounded, spherical smooth calcium hydroxyapatite particles enhance the biocompatibility to the autogenous tissue response into the particle matrix and substantially eliminates the potential for calcification. Jagged or irregular particles can irritate tissue and can cause calcification. In addition, surface porosity on the order of about 30 volume% or greater can also cause calcification because of the relative stability of the pores in the particles. Smooth round, substantially non-porous particles maintain movement in the tissue. Thus, the autogenous tissue grown in the particle matrix where movement is maintained, does not calcify. In contrast, the porous sections of the individual particles are stationary relative to the particle, thus tissue infiltration into the pores is not subject to movement and calcification can occur.

The particulate ceramic material can be suspended in a biocompatible, resorbable lubricant, such as a polysaccharide gel to improve the delivery of the augmentation material by injection to the tissue site where augmentation is desired. Suitable polysaccharides will be readily apparent to one skilled in the art. Polysaccharides that may be utilized in the present invention include, for

example, any suitable polysaccharide within the following classes of polysaccharides: celluloses/starch, chitin and chitosan, hyaluronic acid, hydrophobe modified systems, alginates, 5 carrageenans, agar, agarose, intramolecular complexes, oligosaccharide and macrocyclic systems. Examples of polysaccharides grouped into four basic categories include: 1. nonionic polysaccharides, including cellulose derivatives, starch, guar, 10 chitin, agarose and dextron; 2. anionic polysaccharides including cellulose derivatives starch derivatives, carrageenan, alginic acid, carboxymethyl chitin/chitosan, hyaluronic acid and xanthan; 3. cationic polysaccharides including cellulose derivatives, starch derivatives guar derivatives, chitosan and chitosan derivatives (including chitosan lactate); and 4. hydrophobe modified polysaccharides including cellulose derivatives and alpha-emulsan. Preferred 15 polysaccharides for use in the present invention include, for example, agar methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, microcrystalline cellulose, oxidized cellulose, chitin, chitosan, alginic acid, sodium alginate, and 20 xanthan gum.

The cellulose polysaccharide gels are particularly advantageous because of what can be referred to as their viscoelastic characteristics. Among these characteristics is that of shear thinning. That is, the cellulose polysaccharide gels will flow more readily as forces are applied thereto. This facilitates the ease of mixing when 25

the solid granulate is added to the gel. The shear thinning also permits an easier delivery of the viscous material than would otherwise be the case. Another characteristic of the material is that it is elastic in that it tends to recover its initial shape after being deformed. This is highly significant because the elastic nature of the gel allows for the gel to suspend the augmentation material substantially indefinitely therefore achieving a substantially indefinite shelf life. Materials of relatively high density may be suspended by this gel. For example, calcium hydroxylapatite granulate, spherically shaped with diameters ranging from 75 to 125 micrometers, and with a density of 3.10 g/cc can be indefinitely suspended in a gel with a composition of 14.53 parts glycerin, 82.32 parts water, and 3.15 parts NaCMC.

The elastic characteristics of the gel in accordance with the present invention are further advantageous because the tissue augmentation material and the cellulose polysaccharide gel can be subjected to mixing to suspend the tissue augmentation material in the gel using conventional mixing apparatus without adverse impact on the gel carrier. That is, the gel carrier will not break down or lose its elastic properties. These processes are enhanced by the rate of recovery of gel elastic properties which occurs in a matter of seconds once the hydrated gel has been formed. This rapid recovery of shape due to the elasticity is also highly significant for placement and retention of the material when implanted into living tissue.

The recovery of a more viscous characteristic, once the force of injection is removed, assists in the retention in place of the material, minimizing extravasation.

Any suitable solvent for the cellulose polysaccharide gel may be utilized in the present invention. For example, the gel may be an aqueous cellulose polysaccharide gel. Alternatively, the solvent may be an aqueous alcohol, including for example, glycerol, isopropyl alcohol, ethanol, and ethylene glycol, or mixtures of these. Other suitable solvents for the gel carrier will be apparent to one skilled in the art. Surfactants, stabilizers, pH buffers, and other additives may also be useful, as would be obvious to one skilled in the art. Pharmaceutically active agents, such as growth factors, antibiotics, analgesics, etc. could also be usefully incorporated and would be apparent to one skilled in the art.

In addition, while the present invention has been described herein with respect to a ceramic tissue augmentation material, the cellulose polysaccharide gel carrier of the present invention may also be utilized as a carrier for other tissue augmentation material. For example, the cellulose polysaccharide gel carrier of the present invention may be utilized as a carrier for non-ceramic tissue augmentation material such as, glass, polymethylmethacrylate, silicone, titanium and other metals, etc. Other suitable non-ceramic tissue augmentation material that may be suspended using

the carrier of the present invention will be apparent to one skilled in the art.

The formulation of the gel will depend on a number of factors, including: 1) the molecular weight, degree of substitution, and other properties of the polysaccharide, 2) the solvent system employed, and 3) final properties required for the particular application of the material. In general, the ratio of cellulose polysaccharide to solvent can vary from about 0.5 to 10: 95.5 to 90. For example, in an 85:15 water:glycerin mixture, the ratio is preferably about 1.5 to 5: 98.5 to 95, and most preferably about 2.5 to 3.5: 97.5 to 96.5, respectively.

Preferably, the gel comprises water, glycerin and sodium carboxymethylcellulose. The gel enables the ceramic particles to remain in suspension without settling for an indefinite period of time until used, more specifically, at least about 6 months. Other suitable lubricant compositions known in the art can also be employed.

In general, the ratio of water (or other solvent, e.g. saline, Ringer's solution, etc.) to glycerin in the gel can vary from about 10 to 100:90 to 0, preferably about 20 to 90:80 to 10, and most preferably about 85:15, respectively.

The viscosity of the gel can vary from about 20,000 to about 350,000 centipoise, preferably about 150,000 to about 250,000 centipoise, and more preferably from greater than 200,000 to about 250,000 centipoise as measured with a Brookfield Viscometer with RU#7 spindle at 16 revolutions per

minute (rpm) at 25°C. It has been found that with gel viscosities below about 20,000 centipoise the particles may not remain in suspension, and with gel viscosities above about 350,000 centipoise, the gel 5 may become too viscous for convenient mixing.

In a preferred embodiment of the invention wherein the polysaccharide is sodium carboxymethylcellulose, the sodium carboxymethylcellulose included in the gel has a high viscosity. More specifically, the sodium carboxymethylcellulose preferably has a viscosity of about 1000 to 4000 centipoise, preferably about 10 2000 to 3000 centipoise, in a 1% aqueous solution per a procedure given in Hercules/Agualon Division Brochure 250-10F REV. 7-95 2M, "Sodium 15 Carboxymethylcellulose Physical and Chemical Properties," pp. 26-27. The carboxymethylcellulose content can vary from about 0.25 to 5 weight %, 20 preferably 2.50 to 3.50% of the combined (85 parts) water and (15 parts) glycerin in the gel.

The cellulose polysaccharide gel carrier of the present invention has been discussed in connection with the preferred sodium carboxymethylcellulose gel carrier. However, as discussed above, any suitable 25 polysaccharide gel may be utilized for the carrier in accordance with the present invention, provided it suspends the tissue augmentation material homogeneously therein for a substantially indefinite period of time and possesses the shear thinning and 30 elastic properties described above. More specifically, the polysaccharide gel carrier preferably has the following shear thinning and

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elastic properties: 1) a viscosity of between 1 and  
5 million centipoise when stressed with a shear of  
200 Pascals and a viscosity of 300,000 to 1 million  
cps when stressed with a shear of 500 Pa; 2) an  
5 elastic modulus, under a 100 Pa. maximum force  
measured at 1 hertz, of 50 to 1000 Pa.; 3) a ratio  
of viscous modulus to elastic modulus of 0.2 to 1.0,  
when measured under a 100 Pa. maximum force at 1  
hertz; 4) a recovery of deformation of 5 to 75% after  
10 being subjected to a deformation force of 100 Pa  
for 120 seconds; and, 5) a majority of the recovery  
of the deformation in (4) should occur in 2 to 10  
seconds. The measurements described above can be  
conducted with a controlled stress rheometer, e.g. a  
15 Häake RS100 with a 2 cm. parallel plate, operating  
in stress ramp, oscillatory, and creep/recovery  
modes. The actual values of the shear thinning and  
elastic properties described above will depend on  
the intended application and properties (e.g. size,  
20 density, etc.) of a dispersed particulate.

In the tissue augmentation material and method  
of the present invention, other polysaccharides can  
also be included or used separately such as  
cellulose, agar methylcellulose, hydroxypropyl  
methylcellulose, ethylcellulose, microcrystalline  
25 cellulose, oxidized cellulose, chitin, chitosan,  
alginic acid, sodium alginate, xanthan gum and other  
equivalent materials.

Unexpectedly, formulating the augmentation  
30 particles of the present invention, particularly the  
calcium hydroxyapatite with sodium  
carboxymethylcellulose, provides a change in the

surface morphology of the particles which is believed to enhance the physical and biocompatible properties of the material.

The glycerin in the preferred formulation provides several advantages. First, the composition is more lubricious when glycerin is present. Second, for a given level of polysaccharide gel former, the viscosity is substantially enhanced with some glycerin relative to a pure aqueous gel. Third, the presence of the glycerin minimizes moisture loss of the gel by dessication.

The gel is prepared by mixing the gel components at ambient conditions until all components are in solution. It is preferable to combine the glycerin and NaCMC components together first until a thoroughly mixed solution is obtained. The glycerin/NaCMC solution is then mixed together with the water until all components are in solution to form the gel. After the gel components have been thoroughly mixed, the gel is allowed to set for a minimum of 4 hours, after which viscosity readings are taken to ensure that the gel has the desired viscosity.

While any lubricant or carrier can be employed, it has been found that certain materials, e.g., polysorbate surfactants, pectin, chondroitin sulfate and gelatin, are not able to suspend the ceramic particles for an indefinite amount of time and allow further processing or be as easy to inject in the same manner as the preferred sodium carboxymethylcellulose. Thus, the sodium carboxymethylcellulose materials are preferred.

The preferred polysaccharide gel is biocompatible and able to maintain the particles of ceramic material in what amounts to a substantially permanent state of suspension so that the ceramic particulate/gel composition comprising the augmentation material does not require mixing before use. As already noted, the lubricious nature of the polysaccharide gel reduces the frictional forces generated by transferring the augmentation material from a syringe by injection into the tissue site.

In addition, the polysaccharides do not generate an antigenic response as do products containing amino acids. The polysaccharide gel is readily sterilizable and stable at ambient conditions and does not need refrigeration for storage and shipment, in contrast to systems used with collagen containing materials.

Sterilization is ordinarily accomplished by autoclaving at temperatures on the order of about 115°C to 130°C, preferably about 120°C to 125°C for about 30 minutes to 1 hour. Gamma radiation is unsuitable for sterilization since it tends to destroy the gel. It has also been found that sterilization generally results in reduction of its viscosity. However, this does not adversely affect the suspension and therefore the extrusion force of the augmentation material through a syringe, nor does it affect the ability of the gel to hold the calcium hydroxyapatite particles in suspension, as long as the prescribed viscosity ranges for the gel are maintained.

After injection of the augmentation material into the tissue, the polysaccharide gel is harmlessly resorbed by the tissue, leaving the non-resorbable calcium hydroxyapatite matrix in place in the particular area or bolus, where it has been found to remain without migrating to other areas of the body. It generally takes an average of about 2 weeks for the polysaccharide to completely resorb.

FIGURE 2 shows a histological section of rabbit tissue at 50x magnification which has been infiltrated with autogenous three dimensional, randomly oriented, non-scarring soft muscle tissue as a result of an injection of calcium hydroxyapatite particles having a uniform particle size distribution of 38 to 63 microns. The photomicrograph shows growth after 12 weeks. The histological section also demonstrates the biocompatibility of the calcium hydroxyapatite as the cells grow on the surface of the particles with minimal or substantially no foreign body response.

It has been found that the amount of calcium hydroxyapatite particles in the augmentation material can vary from about 15% to 50% by volume, and preferably about 25% to 47.5% and most preferably about 35% to 45% by volume of the total augmentation material, comprising the gel and the ceramic particles.

Preparations having above 50 volume % ceramic particles become viscous and care should be taken as to the selection of injection apparatus. As a lower limit the augmentation material of this invention should obviously contain a sufficient volume of

ceramic particles to provide an effective base for autogenous tissue growth. For most applications this is at least 15 volume %. By maintaining a volume % of about 35 to 45%, a correction factor of about 1:1 can be achieved, that is, the volume of autogenous tissue growth is roughly equivalent to the volume of particles introduced and shrinkage or expansion at the site of the soft tissue augmentation does not generally occur.

Also, within these parameters, the augmentation material can easily be injected through an 18 gauge or smaller syringe intradermally or subcutaneously. Because of the reduced frictional forces necessary to deliver the biocompatible augmentation material by injection to the desired tissue site, the size of the syringe used to transfer or inject the biocompatible augmentation material can be significantly reduced. This substantially eliminates the possibility of creating a needle trail through which leakage of the augmentation material from the injection site can occur after withdrawing the injection needle. Thus, the syringes used to inject the augmentation material can have reduced openings of less than 1,000 microns in diameter to a minimum of about 178 microns or less.

For example, an 18 gauge syringe having a diameter of about 838 microns, or a 20 gauge syringe having a diameter of about 584 microns, or a 22 gauge syringe having a diameter of about 406 microns, and even a 28 gauge syringe having a

diameter of about 178 microns can be used, depending on the tissue site where augmentation is needed.

The lubricious suspension of augmentation material is prepared by simply mixing the desired amount of ceramic particles with the lubricious gel until a uniform, homogeneous suspension is reached. The consistency of the ceramic particles suspended in the lubricious gel is comparable to strawberry preserves, wherein the seeds and other solid parts of the strawberry, for all practical purposes, are comparable to the ceramic particles and remain substantially permanently suspended in the jelly preserve matrix.

The suspension of ceramic material in the lubricious gel is so stable, that centrifugation at forces on the order of 500g's, that is, 500 times the force of gravity generally do not affect the stability of the suspension or cause it to settle out. The tendency, if any, for particles to settle out over a period of time would appear more likely to occur with the larger particle sizes on the order of 125 microns or larger. Thus, remixing the augmentation material at the time of injection or implantation is ordinarily not necessary. In addition, the polysaccharide gel lubricates the suspended ceramic particles so that the injection force on the syringe can be minimized when injecting the augmentation material.

Tissue augmentation material in accordance with the present invention is particularly advantageous in the treatment of osteoporosis or related pathologies in, for example, the femur, or osseous

defects due to trauma or surgical incision. The advantages of this material in these applications include biocompatibility, ease of application, and a superior result to other materials currently employed.

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Specifically, because the material can be injected through fine catheters and needles, small incision sites such as less than a 4.5 mm hole in the bone site may be used, resulting in minimizing the immediate loss of bone trabeculae--the opposite of the intended longer term result. Because of the smaller needle required for using tissue augmentation material in accordance with the present invention, the hole diameter could be greatly reduced and the depth could also be greatly reduced.

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Particles are held together in the present invention for some time by the gel carrier, even in a liquid environment. In an osseous site, the gel would provide a means of "fixing" the particles for a period of time.

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Furthermore, because the particulate is relatively small, it is distributed more widely in the site of interest via injection. The viscosity of the gel carrier could be tailored to produce either a "thin, runny" consistency media or a "thick, robust" consistency, as desired. This could be done by modifying the content of the other components of the composition including, for example, glycerin and sodium carboxymethylcellulose.

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The particle size of the ceramic particulate in the tissue augmentation material could be reduced for this application. That is, material which could

be used would be a 37 - 63  $\mu\text{m}$  CaHA particulate. The main advantage of a larger size range of particle sizes in soft tissue is to ensure a lack of migration due to cellular mechanisms that could transport the particulate to distant organ sites. The chance of this occurring, however, would be greatly reduced for particulate contained, for example, within a trabecular bone cavity. Also, the fact that CaHA is known to bond to bone further reduces concern of migration.

Also, it has been discovered that tissue augmentation material in accordance with the present invention can be the basis for a unique material useful in implant applications. Specifically, it has been discovered that if tissue augmentation material in accordance with the invention is allowed to dry by exposure to air, it developed some surprising properties. If extruded from a syringe, either directly or through a needle or catheter, a "string" of particles with surprising cohesion and flexibility would result after exposure to air. It was apparent that the material was substantially dehydrated and it is possible to form the material in various shapes or into sheets, as desired. The material may be molded and shaped like clay or carved into shape with appropriate instruments to prepare a preform for implantation. The advantages of this material include cohesion, moldability, and the high concentration of particulate per unit volume.

The following examples show specific embodiments of the invention. All parts and percentages are by weight unless otherwise noted.

5

## EXAMPLES

### Example 1

#### Preparation of the Gel

A mixture of 15% glycerin, 85% water, (based on the combined weight of the water and glycerin) and 3.25% NaCMC (again based on the total of the liquid components) is prepared in the following manner:

9.303 g of glycerin and 2.016 g of NaCMC are combined in a vessel. The mixture is then slowly added to 52.718 g of agitating water in a container large enough for batch size and allowed to mix, utilizing an electric mixer, for 30 minutes at a medium speed. The gel is allowed to set for a minimum of four hours.

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### Example 2

#### Preparation of the Augmentation Composition

Aqueous glycerin/NaCMC gel (44.04 g, prepared in Example 1) are placed in a mixing container large enough for batch size. Smooth, rounded substantially spherical CaHA particles (55.99 g) having a uniform particle size of 75 to 125 microns are thoroughly blended, utilizing an electric mixer, for five minutes at a low speed until all the particles are homogeneously distributed in a uniform suspension in the gel. The blended material is packaged in 3 cc polysulfone cartridges and sterilized in an autoclave for 60 minutes at 121°C.

Example 3

Properties of Augmentation Composition

The gel as prepared in Example 1, and the augmentation medium as prepared in Example 2 are examined by means of a parallel plate rheometer (Häake RS100). Testing includes the measurement of rheological properties as a function of applied stress (stress ramp), deformation at constant stress followed by recovery at 0 stress (creep/recovery), and the measurement of the complex modulus using an oscillating stress within the viscoelastic limit of the composition (frequency sweep). Outcomes demonstrate that the behavior of the gel and augmentation composition, both before and after sterilization, is the same. For example, this is demonstrated in Figure 3, which shows the viscosity of the gel and augmentation material before and after sterilization as a function of applied stress from 10 to 1000 Pascals. The shape of the curves are similar and demonstrate the shear thinning characteristic of this material. Other measured values are given in the following table. The viscosity is determined at 500 Pa in a stress ramp measurement. The elastic modulus is determined under an oscillating force of 100 Pa at 1 hertz. The ratio of the inelastic modulus to elastic modulus,  $\tan \delta$ , is determined under an oscillating force of 100 Pa at 1 hertz. The maximum deflection,  $\gamma_{\max}$ , is determined after 120 seconds of a constant 100 Pa applied stress. The % Recovery is determined

after a relaxation of 200 seconds following 120 seconds of a constant 100 Pa applied stress.

5 Table 1. Rheological results of gel and augmentation materials taken on a Häake RS100 control stress rheometer using 2 cm. parallel plates.

X10<sup>3</sup>(d)

	As Prepared Gel	As Prepared Augmentation Composition	Sterilized Augmentation Composition
Viscosity(Cp) @ 500 Pa stress	603,000	4,610,000	4,340,000
Elastic Modulus (100 Pa @ 1 Hz)	408	2520	2684
$\tan \delta$ (100 Pa @ 1 Hz)	0.461	0.453	0.429
$\gamma_{\max}$	2.227	0.367	0.345
% Recovery	44.99	45.50	46.96

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#### Example 4

##### Preparation of the Gel

A mixture of 25% glycerin, 75% water, and 2.25% NaCMC (based on the combined weight of the water and glycerin) is prepared in the following manner:

15

87.90 g of glycerin and 7.91 g of NaCMC are combined in a vessel large enough to mix the total mass. The mixture is then slowly added to 263.71 g of agitating water in a container large enough for batch size and allowed to mix, utilizing an electric mixer, for 30 minutes at a medium speed. The gel is allowed to set for a minimum of four hours.

20

Example 5

Preparation of the Augmentation Composition

5        Aqueous glycerin/NaCMC gel (38.52 g, prepared  
in Example 1) are placed in a mixing container large  
enough for batch size, Smooth, rounded substantially  
spherical CaHA particles (74.86 g) having a uniform  
particle size of 37 to 63 microns are thoroughly  
blended, utilizing an electric mixer, for five  
10      minutes at a low speed until all the particles are  
homogeneously distributed in a uniform suspension in  
the gel.

Example 6

15      In most instances it takes relatively little  
force to inject or extrude the augmentation  
composition, comprising the polysaccharide  
gel/particulate calcium hydroxyapatite suspension,  
into the air since there is relatively little  
resistance. However, greater forces were necessary  
20      to inject the augmentation composition into tissue,  
and this force is significantly influenced by the  
shape of the particulate material. This was  
exemplified by preparing sterilized suspensions of  
25      polysaccharide gel made of 75% water, 25% glycerin,  
and 2.25% sodium carboxymethylcellulose (based on  
the combined weight of the water and glycerin) with  
various volume percents of calcium hydroxyapatite  
particles having different shapes, following the  
30      procedure of Example 2. The thus prepared  
suspensions were placed in standard 3 cubic  
centimeter syringes. The force applied to the

plunger to extrude the polysaccharide gel/particulate suspension at a rate of one inch per minute through an 18 gauge needle was then measured. The force was also measured with the needle inserted into turkey gizzard tissue as an analogy as it would be used clinically. The spray dried particles of calcium hydroxyapatite, regardless of their shape, had a smooth, uniform appearance under microscopic examination at 40x magnification. The particles were uniformly distributed within the range of particle sizes. The results are tabulated in Table 2, which follows:

Table 2

J. C. S/C

Calcium Hydroxyapatite Particles in the Gel			Force, lbs	
Size, Microns	Particle Shape	Volume. %Solids	Air	Tissue
38 to 63	Spherical/Smooth	35	4.5	6.0
38 to 63	Spherical/Smooth	40	5.9	7.2
38 to 63	Irregular	40	8.0*	9.6*
74 to 100	Irregular/Smooth	37	5.5	>30
74 to 100	Irregular/Smooth	41	>30	>30
74 to 100	Spherical/Smooth	42	4.8	5.5

\*Average. Inconsistent results due to complete obstruction of needle that sporadically occurred during the tests, requiring replacement of needle.

This data correlated with animal experimentation where it was not possible to inject irregular particles into tissue even when the

percent solids were reduced below 25 volume % or a 16 gauge needle was used.

Example 7

5        Sterilized samples of polysaccharide  
gel/particulate calcium hydroxyapatite suspensions  
were prepared using a series of designated particle  
size ranges. The distribution of particles was  
uniform within each range of particle sizes. The  
10      particles were smooth, round calcium hydroxyapatite,  
and the gel had the same constituency as Example 1.  
The calcium hydroxyapatite particles occupied 36  
volume % of the suspension. The extrusion force  
into the air for each suspension containing each  
15      designated range of particle sizes was measured  
using a standard 3 cubic centimeter syringe in the  
same manner as in Example 6. The results are  
tabulated in Table 3, which follows, and demonstrate  
that little difference in the extrusion force occurs  
20      as the particle size increases, as long as the  
particle sizes are uniform and maintained in a  
narrow distribution range.

Table 3

XH. X30

Size Distribution, microns	Extrusion Force, lbs
40-60	2.3
62-74	2.0
40-74	2.6
82-100	2.3
100-125	2.2

125-149	2.4
100-149	2.4

Example 8

Sodium carboxymethylcellulose, water and glycerin in various weight percents were formulated 5 into four different gels following the procedure of Example 1, except for the use of different proportions. Each gel was then blended with about 40 volume % calcium hydroxyapatite particles having a distribution of 38 to 63 microns. The 10 gel/particle blends were then placed in standard 3 cubic centimeter syringes fitted with 18 gauge, 20 gauge and 22 gauge needles. The extrusion force of the blend into the air was measured in the same manner as in Example 3. The results appear below in 15 Table 4.

Table 4

✓ 10/4/30

%NaCMC*	Weight %		Force, lbs		
	Glycerin	Water	18 gauge	20 gauge	22 gauge
1.0	60	40	3.6	6.4	7.7
1.5	50	50	4.0	5.8	8.2
2.0	30	70	4.1	6.3	7.7
2.0	40	60	4.8	7.0	9.2

\*Sodium carboxymethylcellulose. Weight% of sodium 20 carboxymethylcellulose based on total weight of glycerin and water.

Example 9

Preparation of the Augmentation Composition

Using Polystyrene Microbeads

5       A gel consisting of 4.93% glycerin, 93.60%  
water, and 1.48% NaCMC was prepared by methods  
described in Example 1. Spherical polystyrene beads  
(12.79 g), having a particle size range of 100 to  
500 microns are thoroughly blended, utilizing an  
10      electric planetary mixer, for five minutes at a low  
speed until all the particles are homogeneously  
distributed in a uniform suspension in 28.43 grams  
of gel. The polystyrene beads have a density of  
15      1.07 g/cc as measured by helium pycnometry. The  
blended material is packaged in 10 cc polypropylene  
syringe cartridges and sterilized in an autoclave  
for 60 minutes at 121°C. The polystyrene beads  
remained homogeneously distributed within the gel  
carrier. Rheologic properties were measured as  
20      described in Example 3. The viscosity is determined  
at 100 Pa in a stress ramp measurement. The elastic  
modulus is determined under an oscillating force of  
20 Pa at 1 hertz. The ratio of the inelastic  
modulus to elastic modulus,  $\tan \delta$ , is determined  
25      under an oscillating force of 20 Pa at 1 hertz. The  
maximum deflection,  $\gamma_{\max}$ , is determined after 120  
seconds of a constant 10 Pa applied stress. The %  
Recovery is determined after a relaxation of 200  
seconds following 120 seconds of a constant 10 Pa  
30      applied stress. Results are shown in Table 5.

Table 5. Rheological results of gel and polystyrene augmentation material taken using a Häake RS100 control stress rheometer using 2 cm. parallel plates.

5

	As Prepared Gel	As Prepared Augmentation Composition	Sterilized Augmentation Composition
Viscosity(Cp) @ 100 Pa stress	2,050	47,900	9,630
Elastic Modulus (20 Pa @ 1 Hz)	11	31	16
$\tan \delta$ (20 Pa @ 1 Hz)	1.348	1.320	2.067
$\gamma$ max, (@ 10 Pa.)	27.406	5.717	47.873
% Recovery	22.4	23.4	1.6

Example 10

Preparation of the Augmentation Composition

Using Polymethylmethacrylate Microbeads

10 A gel consisting of 9.80% glycerin, 88.24% water, and 1.96% NaCMC was prepared by methods described in Example 1. Spherical polymethylmethacrylate beads (12.78 g), having a uniform particle size of 100 to 180 microns are 15 thoroughly blended, utilizing an electric planetary mixer, for five minutes at a low speed until all the particles are homogeneously distributed in a uniform suspension in 28.84 grams of gel. The polymethylmethacrylate beads have a density of 1.21 20 g/cc as measured by helium pycnometry. The blended material is packaged in 10 cc polypropylene syringe cartridges and sterilized in an autoclave for 60 minutes at 121°C. The polymethylmethacrylate beads

remain homogeneously distributed within the gel carrier. Rheologic properties were measured as described in Example 6. The viscosity is determined at 100 Pa in a stress ramp measurement. The elastic modulus is determined under an oscillating force of 20 Pa at 1 hertz. The ratio of the inelastic modulus to elastic modulus,  $\tan \delta$ , is determined under an oscillating force of 20 Pa at 1 hertz. The maximum deflection,  $\gamma_{\max}$ , is determined after 120 seconds of a constant 20 Pa applied stress. The % Recovery is determined after a relaxation of 200 seconds following 120 seconds of a constant 20 Pa applied stress. Results are shown in Table 3.

15 Table 6. Rheological results of gel and polymethylmethacrylate augmentation material taken using a Häake RS100 control stress rheometer using 2 cm. parallel plates.

X. 0 460

	As Prepared Gel	As Prepared Augmentation Composition	Sterilized Augmentation Composition
Viscosity(Cp) @ 100 Pa stress	58,700	482,000	22,200
Elastic Modulus (20 Pa @ 1 Hz)	58	212	42
$\tan \delta$ (20 Pa @ 1 Hz)	0.785	0.705	1.934
$\gamma_{\max}$	2.895	1.111	0.211
% Recovery	53.1	48.2	20.9

20

Example 11

Preparation of the Augmentation Composition

Using Glass Microbeads

5       A gel consisting of 14.56% glycerin, 82.52%  
water, and 2.91% NaCMC was prepared by methods  
described in Example 1. Spherical glass beads  
(30.42 g), having a uniform particle size of 30 to  
90 microns are thoroughly blended, utilizing an  
10      electric planetary mixer, for five minutes at a low  
speed until all the particles are homogeneously  
distributed in a uniform suspension in 29.27 grams  
of gel. The glass beads have a density of 2.54 g/cc  
as measured by helium pycnometry. The blended  
15      material is packaged in 10 cc polypropylene syringe  
cartridges and sterilized in an autoclave for 60  
minutes at 121°C. The glass beads remain  
homogeneously distributed within the gel carrier.  
Rheologic properties were measured as described in  
20      Example 3. The viscosity is determined at 500 Pa in  
a stress ramp measurement. The elastic modulus is  
determined under an oscillating force of 100 Pa at 1  
hertz. The ratio of the inelastic modulus to  
25      elastic modulus,  $\tan \delta$ , is determined under an  
oscillating force of 100 Pa at 1 hertz. The maximum  
deflection,  $\gamma_{\max}$ , is determined after 120 seconds of  
a constant 100 Pa applied stress. The % Recovery is  
determined after a relaxation of 200 seconds  
following 120 seconds of a constant 100 Pa applied  
30      stress. Results are shown in Table 7. The  
sterilized augmentation material was filled into 3

cc syringe cartridges and extruded through 3.5 inch 20 gauge spinal needles. The average extrusion force was 14.63 lbs. with a standard deviation of 0.09 lbs.

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Table 7. Rheological results of gel and glass augmentation material taken using a Häake RS100 control stress rheometer using 2 cm. parallel plates.

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	As Prepared Gel	As Prepared Augmentation Composition	Sterilized Augmentation Composition
Viscosity(Cp) @ 500 Pa stress	135,000	803,000	569,000
Elastic Modulus (100 Pa @ 1 Hz))	256	699	570
$\tan \delta$ (100 Pa @ 1 Hz)	0.545	0.557	0.692
$\gamma_{max}$	4.302	1.195	3.259
% Recovery	36.3	37.7	24.7

Example 12

Preparation of the Augmentation Composition

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Using Stainless Steel Microbeads

A gel consisting of 4.76% glycerin, 90.48% water, and 4.76% NaCMC was prepared by methods described in Example 1. The mixing time was extended from 30 minutes to one hour for this formulation. Spherical stainless steel beads (95.19 g), having a uniform particle size of 60 to 125 microns are thoroughly blended, utilizing an electric planetary mixer, for five minutes at a low speed until all the

particles are homogeneously distributed in a uniform suspension in 28.69 grams of gel. The stainless steel beads have a density of 7.93 g/cc as measured by helium pycnometry. The blended material is  
5 packaged in 10 cc polypropylene syringe cartridges and sterilized in an autoclave for 60 minutes at 121°C. The stainless steel beads remain homogeneously distributed within the gel carrier.  
10 Rheologic properties were measured as described in Example 3. The viscosity is determined at 500 Pa in a stress ramp measurement. The elastic modulus is determined under an oscillating force of 100 Pa at 1 hertz. The ratio of the inelastic modulus to elastic modulus,  $\tan \delta$ , is determined under an  
15 oscillating force of 100 Pa at 1 hertz. The maximum deflection,  $\gamma_{\max}$ , is determined after 120 seconds of a constant 100 Pa applied stress. The % Recovery is determined after a relaxation of 200 seconds following 120 seconds of a constant 100 Pa applied  
20 stress. Results are shown in Table 8. The sterilized augmentation material was filled into 3 cc syringe cartridges and extruded through 3.5 inch 20 gauge spinal needles. The average extrusion force was 30.84 lbs with a standard deviation of  
25 0.37 lbs.

Table 8. Rheological results of gel and stainless steel augmentation material taken on a Häake RS100 control stress rheometer using 2 cm. parallel plates.

X 11 190  
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	As Prepared Gel	As Prepared Augmentation Composition	Sterilized Augmentation Composition
Viscosity(Cp) @ 500 Pa stress	8,150,000	42,400,000	23,600,000
Elastic Modulus (100 Pa @ 1 Hz)	1663	8411	5085
$\tan \delta$ (100 Pa @ 1 Hz)	0.335	0.366	0.400
$\gamma_{\max}$	0.336	0.110	0.197
% Recovery	62.8	64.5	54.3

### Example 13

#### Preparation of the Augmentation Composition

##### Using a Xanthan Gum Gel Former

5 A gel consisting of 13.8 parts glycerin, and 78.2 parts water, and 8 parts xanthan gum polysaccharide was prepared by methods described in Example 1. The viscosity of the gel, measured using a Brookfield Rheometer, was 51,250 cps. Calcium hydroxylapatite granulate in a range of 75 to 125 microns in diameter are thoroughly blended, utilizing an electric planetary mixer, for five minutes at a low speed until all the particles are homogeneously distributed in a uniform suspension in 15 of gel. The blended material is packaged in polypropylene syringe cartridges and sterilized in an autoclave for 60 minutes at 121°C. The hydroxylapatite particulate remained homogeneously distributed within the gel carrier. Centrifugation 20 of the cartridges in a IEC Clinical centrifuge, Model OM428, at a force of 1016 x g for 5 minutes did not result in a settling of the particulate in the gel carrier. (This result suggests that the

particulated will not settle even over an extended period of time as the elastic limit of the gel will not be exceeded.) The augmentation material was extruded from the syringe cartridges through 1.5 5 inch long 18 gauge needles. The force required was 3.90 lbs.

#### Example 14

##### Preparation of the Augmentation Composition

10     Using a Xanthan Gum Gel Former and Isopropylalcohol  
A gel consisting of 64.4 parts isopropyl alcohol, and 27.6 parts water, and 8 parts xanthan gum polysaccharide was prepared by methods described in Example 1. The viscosity of the gel, measured  
15     using a Brookfield Rheometer, was 37,500 cps. Calcium hydroxylapatite granulate in a range of 75 to 125 microns in diameter are thoroughly blended, utilizing an electric planetary mixer, for five minutes at a low speed until all the particles are  
20     homogeneously distributed in a uniform suspension in of gel. The blended material is packaged in polypropylene syringe cartridges and sterilized in an autoclave for 60 minutes at 121°C. The hydroxylapatite particulate remained homogeneously  
25     distributed within the gel carrier. Centrifugation of the cartridges in a IEC Clinical centrifuge, Model OM428, at a force of 1016 x g for 5 minutes did not result in a settling of the particulate in the gel carrier. (This result suggests that the  
30     particulated will not settle even over an extended period of time as the elastic limit of the gel will not be exceeded.) The augmentation material was

extruded from the syringe cartridges through 1.5 inch long 18 gauge needles. The force required was 7.34 lbs.

Example 15

5       The gel is prepared in accordance with Example 1, and the augmentation medium is prepared in accordance with Example 2. The patient is then appropriately anesthetized and a hole (greater in diameter than an 18 gauge needle) is then drilled  
10      with an entry point in the soft cancellous part of the greater trochanter into the neck, head and trochanteric region of the femur. An 18 gauge needle 3.5 inches long is connected to the syringe containing the augmentation media using the Luer  
15      lock connection. The augmentation media is then injected through the hole in the bone. Sufficient material is injected to serve as a scaffold for bone growth between the particles creating osseous formation and strengthening of the trochanter and  
20      the femoral head of the femur and thus reducing the risk of fracture.

Although the present invention has been described in connection with preferred embodiments thereof, many other variations and modifications and other uses will become apparent to those skilled in the art without departing from the scope of the invention. It is preferred, therefore, that the present invention not be limited by the specific  
30      disclosure herein, but only by the appended claims.